Master thesis

Intermittent vorinostat in BRAF-inhibitor resistant melanoma patients – a headroom analysis

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HEALTH SCIENCES – OPTIMIZATION OF HEALTHCARE PROCESSES

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DATE OF GRADUATION
23/08/2019

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Preface

Healthcare is an increasing area of interest in society nowadays, in which quality, safety and efficiency have become key issues. While novel medical technologies often show potential to improve quality of care, decision makers are challenged to simultaneously embrace medical innovation, and at least delay the increase of the financial burden of healthcare (and especially cancer services) on the national budget. Assessment of health technologies in an early stage of translational biomedical research is therefore of great essence to determine the added value of new interventions and to foster coverage and health system implementation.

This thesis contains a very early Health Technology Assessment (eHTA) of a reused pharmaceutical in the treatment of metastatic melanoma. The study, constructed as a headroom analysis, was conducted from February until August 2019 at the Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital (NKI-AVL) in Amsterdam. The design of the document follows the common structure of a scientific article.

The author would like to thank all contributors to the establishment of this thesis (see ‘Acknowledgement’), which was written as the final assignment to graduate on the master program Health Sciences at the University of Twente.

Clazinus Veijer
Staphorst, August 2019

Intermittent Vorinostat in BRAF-inhibitor Resistant Melanoma Patients – a Headroom Analysis

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Received 23 August 2019

KEYWORDS

Metastatic melanoma;
BRAF inhibitor;
MEK inhibitor;
Drug-resistance;
Vorinostat;
Headroom analysis.

Abstract ***Background*:** Half of BRAF V600 mutated advanced stage melanoma patients treated with BRAF-MEK inhibition develop drug-resistance with around 12 months. A short treatment with vorinostat for two weeks would eliminate the majority of resistant cells, after which BRAF-MEK inhibition is resumed. This treatment cycle can be repeated over time. The novel therapeutic strategy is currently under investigation in a phase I/II study. To analyze the chance of cost-effectiveness in an early stage, a headroom analysis was performed.

***Methods*:** A Markov decision model, consisting of three mutually exclusive health states (on treatment, end-of-life care and death) were modelled to estimate the expected costs and outcomes (quality-adjusted life years; QALYs) for the vorinostat strategy versus the Standard of Care (SoC). For the base case of the vorinostat strategy, a treatment cycle time of 3 months was chosen, with a minimum (+3 months) and maximum (+12 months) expected additional survival to the median overall survival (OS) of the SoC. The sensitivity of the base case to the survival, the additional costs of vorinostat, the incremental quality of life, and the treatment cycle length were analyzed to inform further research prioritization.

***Results*:** A treatment cycle of 3 months, combined with the base case costs of vorinostat and a minimum additional survival, resulted in an ICER of € 20,588/QALY. A maximum additional survival would yield an ICER of € 72,507/QALY. Additional costs of vorinostat could rise to € 4,635 in the minimum and to € 2,465 in the maximum extended survival scenario. A shorter treatment cycle increased the chance of cost-effectiveness.

***Conclusions*:** The results of this very early cost-effectiveness study suggest that the addition of vorinostat may become a cost-effective intervention. The outcome is counter-intuitive though, since an increasing additional survival in the less expensive vorinostat strategy decreases the chance of cost-effectiveness. Further research should focus on the clinical effects of vorinostat, the feasibility to detect resistance in an early phase, and the survival and quality of life of the SoC.

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1. Introduction

During the past decade, several novel FDA-approved agents for the treatment of patients with unresectable or metastatic cutaneous melanoma increasingly showed improved efficacy. Recommended treatments include immune checkpoint inhibitors (anti-CTLA-4 antibody ipilimumab and anti-PD-1 antibodies pembrolizumab and nivolumab), and inhibitors of the mitogen-activated protein kinase (MAPK) pathway (BRAF inhibitors vemurafenib, dabrafenib and encorafenib and MEK inhibitors cobimetinib, trametinib and binimetinib) for patients harboring an activating BRAF V600 mutation, who represent approximately 50% of melanoma patients (1, 2).

Despite its rapid onset of action, half of patients treated with first-line combined BRAF-MEK inhibitors develop drug resistance with around 12 months (3, 4). Immunotherapy is therefore recommended as a first-line treatment, sequenced by BRAF-MEK inhibition in case of progression (1). As a consequence of progression on targeted therapy, the MAPK pathway becomes reactivated and even hyper-active, resulting in relapse and subsequent disease progression (5). One vulnerability of BRAF-MEK inhibitor resistant cells is the induction of reactive oxygen species (ROS). The even further stimulation of abundant production of ROS would lead to significant DNA damage and apoptotic cell death in resistant melanoma cells (6, 7).

A known antagonist of MAPK inhibitors that induces the release of ROS is the histone deacetylase inhibitor (HDACi) vorinostat. Since drug-resistant cells produce abundant amounts of free radicals, vorinostat only targets this tumor cells, leaving the sensitive melanoma cells alive. Promising results were demonstrated after a subsequent treatment with the HDAC inhibitor for two weeks in mice with BRAF-inhibitor resistant melanoma. Moreover, a supplemental pilot study of three patients showed complete depletion of the drug-resistance mutation after vorinostat treatment (6). This founded a new therapeutic strategy for patients who suffer from metastasized melanoma: BRAF-MEK inhibition treatment is administered until disease progression, sequenced by vorinostat treatment for a short period to exterminate the resistant cells, after which MAPK inhibition is resumed. In fact, this sequence could be repeated until vorinostat treatment appears to have insufficient effect. The MAPKi-HDACi sequential treatment is currently being studied in a clinical proof-of-concept trial of 26 patients (NCT02836548). It is expected that the intermittent use of vorinostat in patients with resistance to BRAF-MEK inhibitors will extend overall survival, compared to continuation of BRAF-MEK blockade after progression (6).

Quantifying the health economic impact of the addition of vorinostat to metastatic melanoma treatment can be part of further fundamental research on the chance of becoming a cost-effective intervention. However, no survival data of vorinostat sequencing targeted therapy in melanoma have been published thus far; even preliminary results of the ongoing phase I study (hereafter: 'vorinostat trial') at the Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital (NKI-AVL) are unknown yet. Also potential quality of life (QoL) consequences and costs of vorinostat are lacking at the moment. Therefore, the hypothetical incremental costs and effects of possible scenarios of vorinostat in clinical use were compared to the standard of care (SoC). The study aimed to inform researchers about the thresholds for a potential cost-effectiveness of intermittent treatment with vorinostat.

Research question
What is the potential cost-effectiveness of the intermittent use of vorinostat, compared to continuation of BRAF-MEK inhibition after drug-resistance in melanoma patients?
What is already known about this topic
• Metastatic melanoma is a severe and costly condition; • The optimal sequence of therapy agents in systemic melanoma treatment is unclear.
What this study adds
Intermittent vorinostat treatment seems to be cost-effective in comparison to BRAF-MEK inhibition among BRAF-inhibitor resistant melanoma patients at a willingness-to-pay of € 80,000 per QALY from a Dutch healthcare perspective.

2. Methods

2.1 Model description

The strategies compared in the analysis, both starting with a population of individuals suffering from BRAF-MEK inhibitor resistant melanoma, were: 1) current standard of care ("SoC"), and 2) additional vorinostat to the standard intervention with intermittent dosages ("vorinostat").

Since the vorinostat strategy lacks any data on survival, QoL and the additional costs of vorinostat, the main drivers that probably would affect the chance of cost-effectiveness of the new therapeutic strategy were identified (see Fig. 1). 1) the effect of vorinostat in terms of the rate of eliminated resistant cells would reasonably affect the response to BRAF-MEK inhibitors (and an assumed correlated survival). 2) An early detection of drug-resistance would lead to a timely treatment with vorinostat, resulting in a higher rate of eliminated resistant cells. 3) The number of cycles with vorinostat per year, which is likely influenced by a prolonged progression free survival (PFS) on BRAF-MEK inhibition, will affect the costs and effects of the intervention. 4) The additional costs of vorinostat to the current costs of BRAF-MEK inhibitors will impact the ratio of costs and effects as well. 5) A fifth driver of cost-effectiveness would be a diminished or accumulated quality of life as a consequence of vorinostat treatment. Common side effects identified this far in the vorinostat trial are fatigue and nausea, however it is unknown to what extent QoL can be distinguished from the SoC.

A correlation between the reset rate of vorinostat and the increased response and survival to BRAF-MEK inhibition is unknown this far; this outcome could probably be derived from the vorinostat trial. The length of the treatment cycle 'vorinostat – BRAF-MEK inhibition' and the survival were therefore the only considered parameters in the analysis to draw plausible scenarios on, based on expert opinion.

A time of three months was chosen as the time between two vorinostat cycles (See Fig. 2). The *extended* overall survival (OS) of patients in the vorinostat strategy compared to the SoC was expected to amount a minimum of 3 and a maximum of 12 months, representing a worst-case

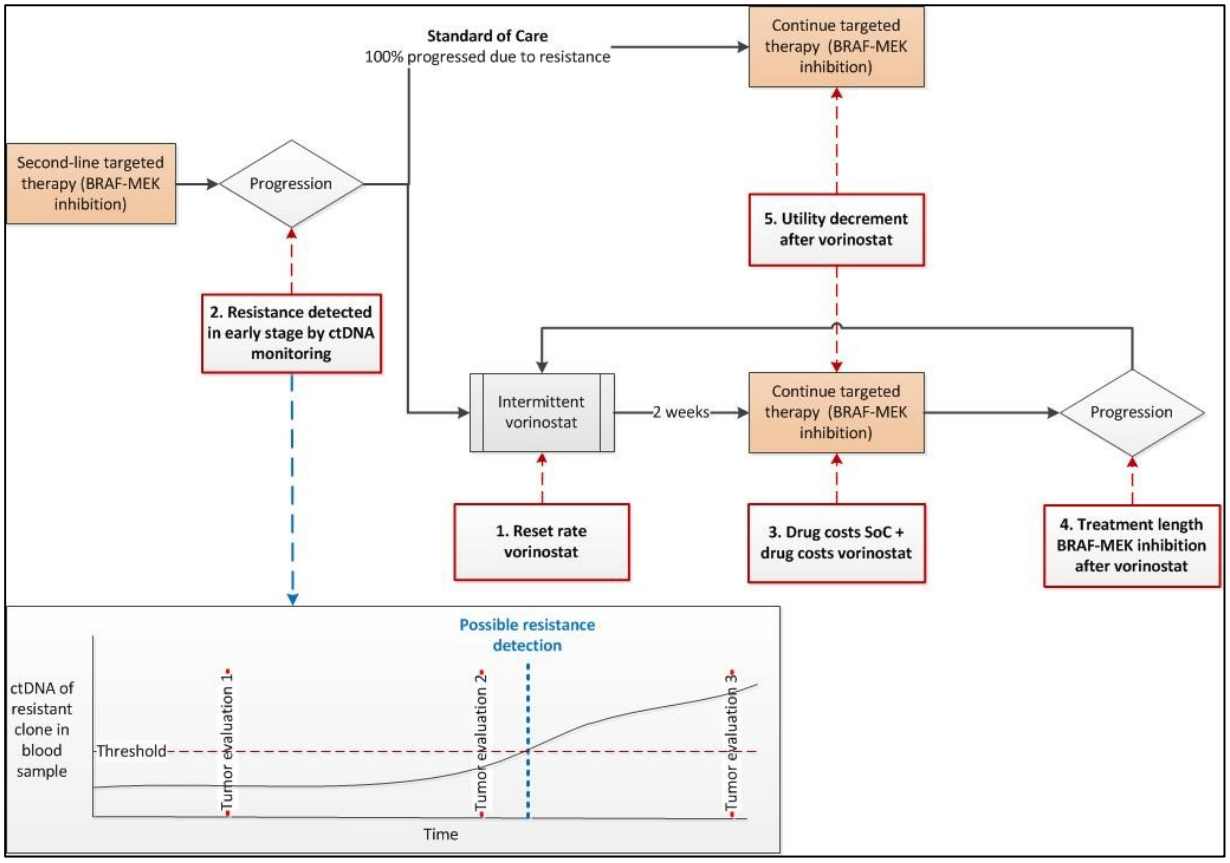


Fig. 1 Five main drivers of cost-effectiveness along the treatment pathway which were thought to influence the chance of cost-effectiveness of vorinostat. A visual representation of the potentiality to screen the ctDNA more frequently is shown at the bottom left side.

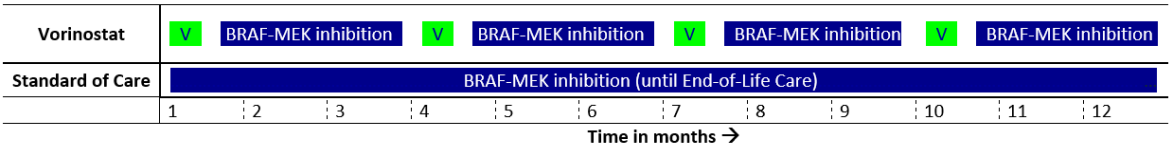


Fig. 2 Schematic overview of treatment sequences over one year for the standard of care and the vorinostat strategy. Green boxes represent intermittent treatment with vorinostat for two weeks.

scenario and a best-case scenario regarding the gain in life years (LY), respectively. If the new drug would not result in an additional survival of at least 3 months, the implementation of vorinostat was thought to be unfeasible, irrespective of its potential cost-effectiveness. The 3 months extended survival is also the cut-off value used for the clinical trial. The base case survival parameter consisted therefore of the minimum and maximum expected additional median OS to the SoC.

2.2 Treatment comparison

According to the common sequence in the Antoni van Leeuwenhoek (AVL) hospital and the NCCN guideline for cutaneous melanoma, second-line targeted therapy is started after the occurrence of progressed disease on first-line immunotherapy with pembrolizumab, whether or not combined with nivolumab (see Supplementary material 1).

Generally, for patients of whom disease progresses (i.e. drug resistance) on second-line targeted therapy, further treatment consists of two options; a) treatment interruption, and b) continuation of treatment beyond progression. An interrupted treatment for several months ('drug holiday') would lead to a transient pause in tumor growth and re-sensitization to MAPK inhibitors (8-10). Continuation of BRAF-MEK inhibition after detected progression, without any interruption, was considered as the SoC in the analysis, though the common strategy for treatment beyond progression in the Netherlands is unclear. Treatment beyond progression is continued until unacceptable toxicity is experienced, or a patient's preference or a physician's reluctance to continue therapy result in treatment discontinuation. Dabrafenib (150 mg twice a day) plus trametinib (2 mg once a day) were selected drug combinations, since it is currently the most used combination in the AVL hospital.

Regarding the vorinostat strategy, drug-resistant patients would switch to an intermittent treatment with vorinostat for two weeks to purge the resistant clone, sequenced by BRAF-MEK inhibition. The newly developed capsules used in the vorinostat trial contain 90 mg vorinostat per capsule. The HDAC inhibitor will be prescribed at a dose of 360 mg once a day, followed by dabrafenib – trametinib at similar doses as in the SoC. After each time of progression on BRAF-MEK inhibitors, the treatment cycle is repeated, starting with vorinostat treatment for two weeks to kill the majority of resistant cells, and sequenced by BRAF-MEK inhibition.

2.3 Model structure

To analyze the long-term incremental net benefit of the additional use of vorinostat in BRAF-inhibitor resistant melanoma treatment, a hypothetical cohort of 1000 patients with metastatic melanoma was simulated, using a Markov state transition model (See Fig. 3). The model comprised of three health states: the BRAF-MEK inhibitor 'treatment beyond progression' (TBP), 'end-of-life care' (EoLC) and 'death'. The target population in the analysis starts in the health state 'TBP' at time t=0, reflecting continuation of treatment for both strategies, after progression has been clinically observed. It was assumed that all patients fall into the 'EoLC' state whenever treatment was discontinued. Patients were thought to spend one month on average in the EoLC state, which represents terminal care. After one month, patients fall from the EoLC state in the absorbing health state 'death'.

The model has a 5-year time horizon, representing the maximum expected life-time of the analyzed patient population. A monthly cycle time was chosen to calculate costs and (quality adjusted) life-years (QALYs) as accurate as possible. The analysis was performed from a Dutch healthcare perspective.

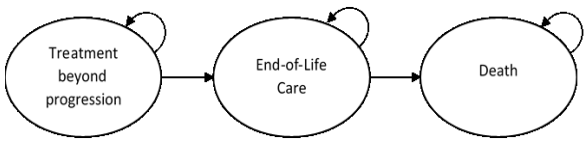


Fig. 3 Markov state transition model with a cycle time of one month.

2.4 Transition probabilities

OS data was used to calculate the transition probabilities between the Markov states. Survival estimates of treatment beyond progression on BRAF-MEK inhibition are very scarce. Although two reviews on the topic of re-challenge with BRAF and/or MEK inhibitors showed response and PFS data, OS data after retreatment was lacking (11, 12).

One of the reviewed studies, a multi-institutional retrospective study by Valpione et al., evaluated the effects of retreatment with different BRAF and/or MEK inhibitors (65% of re-challenge drugs combined with MEKi, dabrafenib – trametinib in 50% of regimens) (13). The study included 116 patients with progressed BRAF-mutated melanoma, of which 83 patients received immunotherapy between initial BRAF-inhibitor treatment and re-challenge. A median OS of 9.8 months (95% CI 0.2 – 34.4) was reported.

The monthly rate of OS for the SoC was calculated by the natural logarithm of the median OS (=0.5), divided by 9.8 months. The monthly rate of treatment discontinuation (one month before death) was calculated as

$$r = -\mathrm{LN}(1 - 0.5)/(\mathrm{OS} - 1)$$

with OS as the median OS in months for the SoC and vorinostat. The monthly probabilities were calculated by exponentiating the rates.

A median OS of 12.8 and 21.8 months applied to the vorinostat strategy, indicating the minimum acceptable and maximum expected median OS, respectively. The probability of OS and treatment continuation (on treatment, OT) and all other base case parameters are shown in Table 1.

2.5 Utility estimates

Effectiveness of treatment was measured in QALYs, which were calculated as the sum of the product of the mean utility of each health state and the mean duration of that state (18). EQ-5D based utilities of targeted therapies in advanced melanoma patients are scarcely re-

Table 1 Input parameters for the base case and the survival scenarios in the vorinostat strategy.

Parameter	Mean	SE	Distribution	Source
1-month survival probabilities				
SoC				
OS	0.932	0.022	Beta	(13)
OT	0.924	0.023	Beta	(13)
Vorinostat				
OS (+3 months, +12 months)	0.947 - 0.969	0.020 - 0.016	Beta	Expert Opinion
OT (+3 months, +12 months)	0.943 - 0.967	0.021 - 0.016	Beta	Expert Opinion
Utilities (EQ-5D scores)				
SoC				
OT	0.834	0.05	Beta	(14)
EoLC	0.444	0.05	Beta	(14)
Vorinostat				
OT	0.834	0.05	Beta	Assumption
EoLC	0.444	0.05	Beta	Assumption
Costs per month (€)				
SoC	13,711.00	1,749.00	Gamma	(15)
Vorinostat*	11,926.00	1,713.00	Gamma	(15)
Vorinostat drug costs‡	1,500.00	-	-	Expert Opinion
Follow-up costs on treatment	115.00	15.00	Gamma	(16)
EoLC costs	5723.00	730.00	Gamma	(17)

* assuming 4 treatment cycles per year.

‡ base case drug costs per cycle of vorinostat for 2 weeks.

SE= Standard Error. SoC = Standard of Care. OS = Overall Survival. OT = On Treatment. EQ-5D = EuroQol 5D. EoLC = End of Life Care.

ported; one article published EQ-5D utility scores in the COMBI-v study, a clinical trial of first-line BRAF-MEK inhibition (19). Because of the expected deterioration in a patient's condition at the time of treatment beyond progression on second-line therapy, the utility score of the COMBI-v study was not used in the analysis.

Alternatively, a meta-analysis identified the utility of melanoma patients at different stages of disease, specified by type of treatment (14). For patients with stage IV melanoma treated with targeted therapy, the mean EQ-5D utility score was 0.834 (95-% CI 0.822-0.846).

The utility of the EoLC state was derived from a cost-effectiveness analysis of immunotherapy, reporting utility measures until time of death. A mean utility of 0.480 (95-% CI 0.35-0.61) applied at the time of less than 30 days until death (20).

Utilities for the vorinostat strategy are lacking and were assumed to be equal to the SoC.

Quality of life was assumed to be constant over time within each health state (i.e. a single utility value applies to that health state).

2.6 Costs

A healthcare perspective was used in the analysis, meaning that direct healthcare costs only are taken into account. Economic inputs included drug costs, follow-up costs, and EoLC costs. Costs of BRAF and MEK inhibitors were based on Dutch official pharmaceutical prices (15). For a base case, the costs of vorinostat were estimated to be € 1,500 per patient per treatment of two weeks, based on expert opinion of the pharmacy (NKI-AVL).

Costs of follow-up consisted of a three monthly visit at the oncologist, including a radiological assessment (CT scan) to detect progression or resistance, and serum S100B testing. Specific costs of EoLC are very heterogeneous. As these costs are out of focus in the analysis, the public price of the AVL hospital for palliative inpatient care was taken as a proxy for the one-month costs of EoLC (17). All costs in Euros were inflated to Dutch 2019 price levels.

2.7 Analysis

The analysis was modeled and visualized using MS Excel. Costs and utilities were discounted by a rate of 4% and 1,5%, respectively, which is in concordance with the Dutch guideline for economic evaluations in healthcare (21). A deterministic analysis of the base case values was conducted to derive the LYs, QALYs and costs for both strategies, and the Incremental Cost-Effectiveness Ratio (ICER).

One-way sensitivity analyses were conducted to identify the impact on the ICER in costs per quality-adjusted life year (QALY) of four input parameters. First, the survival parameter was varied over a 1 to 24 month additional survival range to derive the development of the ICER over a changing survival. Second, the drug costs of vorinostat were varied with steps of € 1,000 on a range of zero to € 6,000. By varying the additional costs of the vorinostat strategy in the model, the ICER in costs per QALY gained were generated for each cost variation. The maximum reimbursable price (MRP) of the HDAC inhibitor is determined at an ICER of € 80,000, which is the Dutch specific Willingness-To-Pay (WTP) threshold. Third, the sensitivity of the ICER on the QoL parameter was analyzed. The EQ-5D utility score for the 'on treatment' health state for the vorinostat strategy varied in steps of 0.01 over a -0.1 to +0.1 range. Fourth, the monthly costs of the vorinostat strategy depend on the duration of treatment on BRAF-MEK inhibitors. The length of treatment in months until the next required vorinostat treatment was therefore varied over a 1 to 7 months range, at different cycle costs of vorinostat.

Next to the deterministic scenario analysis, a Monte Carlo simulation with 5,000 iterations for both the minimum and maximum extended survival was performed to evaluate variation in multiple parameters at once. Utilities were varied over their 95% confidence interval on a beta distribution. Drug costs were varied within a 25% range of the base case values on a gamma distribution. For the survival parameter, a hypothetical standard-error and 95%-CI for a normal distribution were generated, because of the wide CI of the survival study, which would likely outbalance probabilistic results. Base case costs of vorinostat were used in the probabilistic analyses. To illustrate the uncertainty surrounding the base case estimate of cost-effectiveness, a Cost-Effectiveness (CE) plane and Cost-Effectiveness Acceptability Curves (CEAC) for both survival scenarios were generated.

3. Results

3.1 Base case results

For the SoC, the model outcome showed a mean total LY of 1.12 and 0.74 QALY, with a total cost per patient of € 127,658. Assuming a treatment cycle time of 3 months, an extended median OS of 3 months, and the base case drug cost of vorinostat, the vorinostat strategy resulted in 1.44 LY and 0.93 QALY. The total costs per patient amounted € 131,521 for the minimum extended survival scenario. An extended median OS of 12 months with similar treatment cycle time and vorinostat drug costs resulted in 2.20 LY and 1.35 QALY, with a total cost per patient of € 171,600. The ICER for the minimum and maximum median OS were € 20,588 and € 72,507, respectively.

3.2 Sensitivity analyses

Survival parameter

The output of the first sensitivity analysis illustrates the relation between costs and effects over a changing survival estimate. Over a range of 24 months, the ICER increased substantially over the first 3 months of extended survival (See Fig. 4). The slope of the ICER stabilized after 12 months and did not cross the WTP threshold after 24 months.

Maximum Reimbursable Price

With a 3 months additional survival for the vorinostat strategy, the ICER in costs/QALY crossed the threshold of € 80,000 at a MRP of € 4,635. For the 12 months extended survival, a MRP of € 2,465 was found (See Fig. 5). To keep the new intervention below the WTP threshold, the annual maximum additional costs of vorinostat per patient should not rise above € 18,540 for the minimum and € 9,860 for the maximum extended survival scenario.

Utility of vorinostat

Ceteris paribus, the utility score could decrease by 0.1 and remain below the WTP threshold for the 3 months additional survival. It turned out that the vorinostat strategy in the 12 months extended survival could bear a utility change of at most -0.03 to remain cost-effective (See Fig. 6).

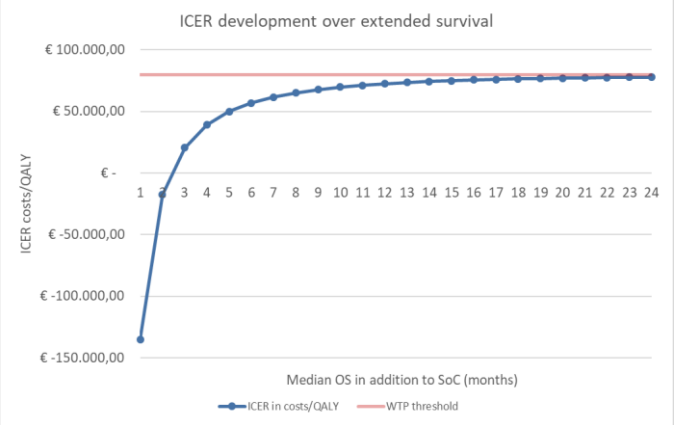


Fig. 4 Slope of the Incremental Cost-Effectiveness Ratio (ICER) over a changing median overall survival parameter in the vorinostat strategy. The red line displays the Willingness-To-Pay threshold.

Fig. 5 ICER in costs per QALY gained for different vorinostat drug cost categories, resulting in the maximum reimbursable price (MRP), projected for the +3 months extended survival and the +12 months extended survival. The red line displays the Willingness-To-Pay threshold.

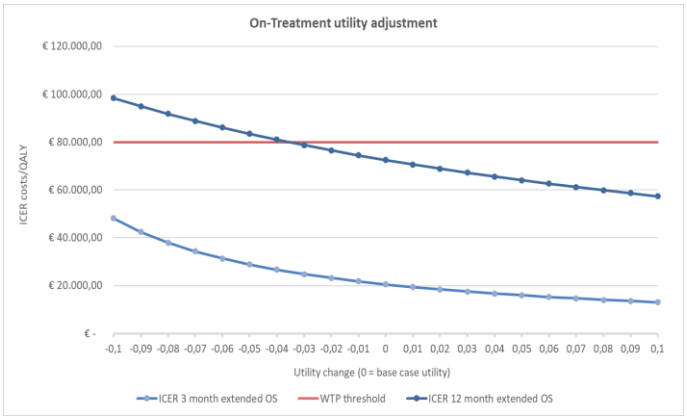


Fig. 6 ICER at varying EQ-5D utility scores of the 'on treatment' health state in the vorinostat strategy. Point '0' indicates the base case utility value, at which the utility of both strategies are equal. Deviation from zero indicates the change in utility score for the vorinostat strategy, in comparison to the utility score of the Standard of Care.

Length of treatment cycle
An increasing cycle length results in an increasing ICER for the vorinostat strategy. For the maximum additional survival, a sequence length of 4 months or higher would require a cost reduction for the vorinostat below the base case cost in the analysis (See Supplementary material 2).

3.3 Uncertainty

The CE plane for the +3 and +12 months median OS represents the uncertainty surrounding both scenarios in the analysis (see Fig. 7). 26% of the bootstrap replicates for the minimum survival were in the dominant quadrant (south-east), while 52% was in the north-east quadrant. For the +12 months survival scenario, the major part (86%) of the cloud was in the north-east quadrant, indicating higher QALYs and increased cost for the vorinostat strategy, compared to the SoC. The diamonds in the clouds indicate that the mean cost-effectiveness of vorinostat for both scenarios is below the WTP-threshold.

The CEACs in Fig. 8a and b show an increasing probability of cost-effectiveness for vorinostat as the WTP threshold goes up. For the minimum survival scenario, the line of vorinostat outweighs the line of the SoC at a threshold of € 27,000 and at a WTP threshold of € 80,000, the probability of cost-effectiveness is approximately 70%. For the maximum survival scenario, both lines crossed at a threshold of € 70,000 and, at the Dutch specific WTP threshold, the probability that vorinostat is cost-effective in comparison to the SoC is ~60%.

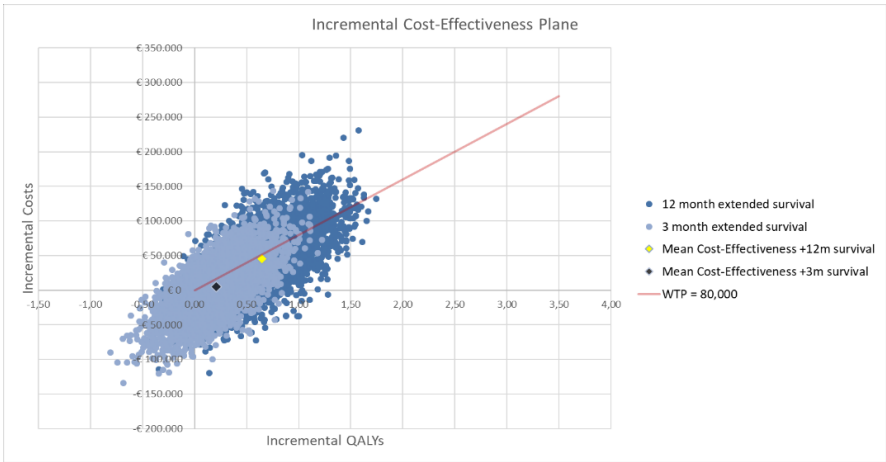
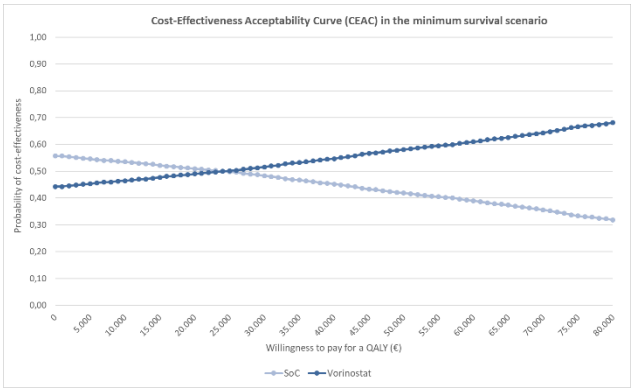
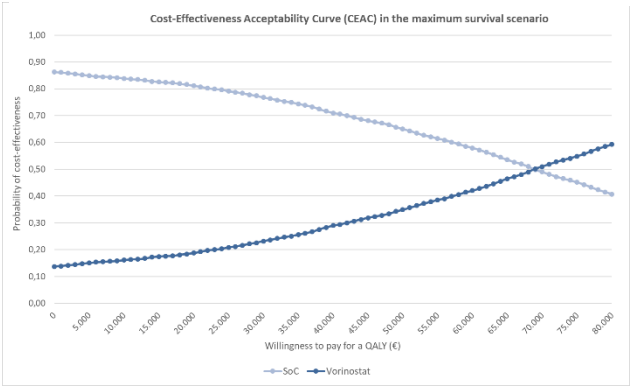


Fig. 7 Cost Effectiveness plane of the incremental costs and QALYs of the vorinostat strategy compared to the standard of care. The scatter plot shows a total of 10,000 iterations for a situation with an additional median overall survival of 3 months and 12 months.



8a: minimum survival scenario



8b: maximum survival scenario.
Fig. 8 Base case Cost-Effectiveness Acceptability Curves (CEAC). The probability of Cost-Effectiveness is presented for a range of values of thresholds.

4. Discussion

The output of this model-based headroom analysis reflects the likelihood of cost-effectiveness of the additional clinical use of vorinostat in a very early stage. Of note, the reported outcomes are dependent on several intercorrelated cost-effectiveness drivers, as described in the method section. Moreover, the results are built on survival and QoL data gathered from various sources with low levels of evidence. The high level of uncertainty makes it difficult to state definitive conclusions about the feasibility and potential cost-effectiveness of the new intervention.

The model outcomes show some counter-intuitiveness: an increasing clinical effectiveness (i.e. increased survival) in the less expensive vorinostat strategy leads to an increasing ICER (i.e. less cost-effective), and vice versa. The NICE appraisal committee did find counter-intuitive results as well from a cost-effectiveness

model of the treatment with BRAF-MEK inhibition (22). The committee concluded that those results reflect the lack of a direct modelled relationship between PFS and OS. In the current analysis, no clear explanation of the counter-intuitive result was found, except for the fact that the patient population in the vorinostat strategy would live longer and consume more healthcare than the population in the SoC. For the minimum survival scenario, costs of vorinostat are slightly higher than the SoC; QALYs are relatively high. As the extended median OS for vorinostat increases to 12 months, incremental costs are 11 times higher, compared to the minimum survival scenario, whereas incremental QALYs are approximately 3 times higher (see also Supplementary material 3).

The outcome of the deterministic analysis showed that the vorinostat strategy seemed to be a cost-effective intervention at both an extended survival of 3 and 12 months, and considering a 3-monthly treatment cycle and the base case additional costs of vorinostat.

Results of the sensitivity analyses represented the sole effect of one parameter on the deterministic model outcome. The decline of the increasing slope of the ICER after a 12 month OS extension was thought to be due to the 5-year time horizon used in the analysis, which is relatively short for an additional median OS of more than 12 months: total costs will not change severely in the first five years when survival rises above a certain value.

The MRP for both scenarios were higher than the estimated cost in the base case. However, it should be noticed that several cost items, including packaging, manufacturing, registration of the new pharmaceutical, additional costs of (more frequent) tumor evaluations, etc. will be incorporated in the (unit) cost of the vorinostat drug. Costs of the vorinostat drug should therefore not be interpreted as sole costs for the active pharmaceutical ingredient and excipient compound of the finished pharmaceutical product. If the additional costs of vorinostat would rise above the MRP, a cost reduction of BRAF-MEK inhibitors can be an alternative option to keep the new intervention cost-effective.

The alteration in the ‘on treatment’ utility of the vorinostat strategy displayed the effect on the ICER if the utility score for both strategies would differ from each other. As a consequence of the increased ICER for the maximum survival scenario, the EQ-5D utility score of patients treated with vorinostat should not decrease substantially, in order to keep the ICER below the WTP threshold.

A diminishing treatment cycle length in the vorinostat strategy leads to a more cost-effective intervention. Because the vorinostat treatment for two weeks is less expensive than BRAF-MEK inhibition for two weeks, a more frequent use of the vorinostat drug leads to lower treatment costs, within a certain time frame.

The probabilistic analysis showed slightly favorable results for the vorinostat strategy, which more or less confirmed the outcome of the deterministic analysis. However, the confidence interval for the survival parameter has been generated hypothetically. The uncertainty of the analysis is visualized by the wide spread of the bootstrap replicates in the CE plane. Looking at the CEACs, it should be addressed that there is substantial uncertainty regarding the cost-effectiveness of vorinostat at a WTP of € 80,000 for both scenarios.

The main limitations of the analysis are affiliated with the lack of real-time data of the vorinostat arm, and the scarcely reported evidence on second- or third-line BRAF-MEK inhibition in melanoma care. Though the pivotal trials showed results at a high level of evidence, survival and quality of life were thought to be negatively influenced by a declining condition of patients during their treatment beyond progression on second-line therapy, together with a higher chance of toxicity in the advanced stage of the disease. The survival data and quality of life measures should be similar to a third-line treatment, in order to reflect a real-world situation. The study of Valpione et al. consisted of patients that received immunotherapy between their initial BRAF-inhibitor treatment and re-challenge, in contrast to the SoC in the analysis, which involves treatment beyond progression without any interrupting therapy. The incorporated utility score originating from the study of Tran et al. was mainly based on first-line therapies, meaning that utilities and QALYs should be interpreted with caution.

Dose modifications - as a consequence of adverse events - were not incorporated in the analysis. Drug costs would likely have been overestimated in this way. Even though the source of drug costs provides rather exact costs of pharmaceuticals, the monthly drug costs of the BRAF-MEK inhibitors in this study should therefore be interpreted carefully. Meanwhile, adverse events and correlated dose modification would cohere to a diminished utility as well,

wherefore the interpretation of QALYs need the same caution. Concerning the drug costs of different BRAF-MEK inhibitor combinations, there is a negligible difference (+2%) between the dabrafenib - trametinib combination and the recent reimbursed BRAF-MEK combination encorafenib - binimetinib. According to the experts at the AVL, the latter combination will be used more often in the near future, supported by the claim of more efficacy and less toxicity of encorafenib - binimetinib compared to previously approved combinations (23). Thus, regarding its drug costs, a potential use of the most recent combination in the near future would be proportionate to the SoC in the analysis.

The first step in a further investigation of the feasibility of the intervention should focus on the anti-tumor response of vorinostat on BRAF-MEK inhibitor resistant patients. The phase I/II vorinostat trial is expected to provide the first evidence on the effect rate of the drug, with a low level of evidence though. Once the clinically added value of vorinostat is known, the direction of further research can be mapped out.

Furthermore, an urgent subsequent step is determining the actual design of the SoC. The potential cost-effectiveness of the vorinostat strategy depends on the type of treatment after progression on second-line BRAF-MEK inhibition. If the SoC would involve a drug holiday, which is supported by limited prove of effectiveness, the chance of cost-effectiveness of vorinostat straight after the detection of a progressed disease would be reduced severely. The specific vulnerability of resistant cells, which is the target of vorinostat, is not or less present after a certain period of treatment interruption (i.e. drug holiday). The nationwide treatment modality used as the SoC should therefore be ascertained in the early stages of the research and development process. Moreover, if a patient's disease remains stable after BRAF-MEK inhibition for a long time (i.e. one year), a maximum length of treatment could be determined. However, most patients at their third-line therapy have a severely deteriorated condition, which reduces the chance of reaching the end of treatment in good health.

The chance of vorinostat as a successful treatment would reasonably increase if resistant cells can be attacked prematurely. The proof-of-concept trial uses a monthly follow-up, at which the cell free tumor DNA in the blood is analyzed as a clinical biomarker, next to the periodical radiological assessment. By monitoring for early signs in the DNA of resistance to BRAF-MEK inhibitors, treatment can be switched back to vorinostat earlier. Researchers should investigate the diagnostic accuracy, but also the clinical and monetary benefits of the use of a biomarker test in future clinical practice.

Clinical use of vorinostat could facilitate a switch in the optimal sequence as it is formalized to date. Treatment initiation with anti-PD1 + anti-CTLA-4 turned out to be more cost-effective than initiation with BRAF+MEK inhibitors, most likely because of the short PFS associated with targeted therapy (24). If the ongoing vorinostat-trial (and further supporting research) indicate a clinically beneficial effect to overcome the relatively short period towards resistance to targeted agents, a cost-effective use of BRAF-MEK blockade as a first-line treatment option becomes more considerable. This shift in treatment sequence would also depend on the availability of biomarkers that predict response and treatment failure to BRAF-MEK inhibition (1).

Next, a thorough specification of the eligible patient population for intermittent vorinostat treatment on both the supply and demand side of the healthcare market for metastatic melanoma treatment is an essential part of further research. Regarding the demand side, researchers should discuss questions like whether patients showing no or limited response to BRAF-MEK inhibitors at their first time, would be eligible to receive vorinostat (and subsequent BRAF-MEK inhibition). Regarding the supply side, a sufficient provision of vorinostat after (a nationwide) access to the pharmaceutical market should be analyzed in a small business case. To date, vorinostat is an off-patent drug, and the pharmacy of the NKI-AVL is able to produce small amounts of the pharmaceutical. If the therapeutic strategy would be applied on a national level, the capacity of the pharmacy to provide vorinostat is likely to be insufficient. Consequently, production of vorinostat will probably be outsourced to a (small) pharmaceutical company. This might lead to additional costs for the new drug and endanger a potentially cost-effective treatment.

As a final recommendation to researchers, the possibility to use vorinostat as an off-label pharmaceutical should be discussed among relevant stakeholders. Vorinostat has a safe pharmacological profile in the clinic and has been approved by the FDA in 2006 for the treatment of progressive cutaneous T-cell lymphoma (CTCL). However, the European Medicines

Agency (EMA) did not approve vorinostat for this indication thus far (25).

Once the major parameters (survival, QoL, costs) would become more certain, a more comprehensive Health Technology Assessment (HTA) can be conducted. Regarding the design of a full cost-effectiveness analysis, the choice around whether to use patient-level or cohort modeling mainly depends on the research question, the heterogeneity of the patient population and any particular patient characteristics that directly influence costs and QALYs. Individual prognostic factors of patients could include the baseline LDH level, the number of organ sites with metastasis, and the number of vorinostat cycles over time. An elevated baseline LDH level is known as a highly predictive factor of patient outcomes, together with the number of involved organs (3, 4). More hypothetically concerning the vorinostat strategy, a rising number of treatment cycles would decline the response to BRAF-MEK inhibitors. As the impact of these predictive factors for patients in the final stage of disease are unknown yet, cohort modeling is recommended for a subsequent analysis. Moreover, microsimulations take longer to build, verify and validate and might be less transparent. Eventually, when using a cohort state transition model, subgroup analyses can still be performed to find a relationship between patient characteristics and model outcomes. Concerning the state transition model in a reassessment of the analysis, the mathematical construction and the added value of a one-month EoLC health state should also be critically revised and discussed.

Alongside the economic evaluation, a Value of Information (VOI) analysis should clarify the financial needs and optimal design of additional research. Assessing the return on investment can convince funders of research to support further investigation. The principles of a VOI can identify the efficient sample size for a future trial, and the expected value of perfect information (EVPI) would reveal how much costs will have to be spent in order to gain access to perfect information.

5. Conclusion

The results of this very early analysis on the potential cost-effectiveness suggest that the addition of vorinostat to the treatment of BRAF-mutated melanoma patients of whom disease progresses on second-line BRAF inhibitor therapy has a considerable chance of cost-effectiveness. The outcome has a counter-intuitive property, though: a minimum extended survival reflects a higher chance of cost-effectiveness, compared to a maximum extended survival, while the new intervention is less costly than the SoC. Because of the high uncertainty of input parameters, it is important to note that the analyzed data is purely informative and should not serve as a basis for clinical decision making.

Further research especially needs to declare the anti-tumor response of vorinostat and the feasibility of using a clinical biomarker to detect drug-resistance in its early stage, but should further specify the survival and QoL of the SoC as well. When this new evidence becomes available, reassessment of the cost-effectiveness of vorinostat in patients with BRAF-inhibitor resistant melanoma should be carried out.

Conflict of interest statement
None declared.

Acknowledgements
The author would like to acknowledge cooperating clinicians and researchers (dr. S. Wilgenhof, S. Huijberts, and prof. dr. R.A. Bernards) at the NKI-AVL for their expert opinion input. The author would like to acknowledge prof. dr. W.H. van Harten and dr. V.P. Retèl for their substantial contributions in the concept, design and coordination of the study, and their support to draft and revise the manuscript.

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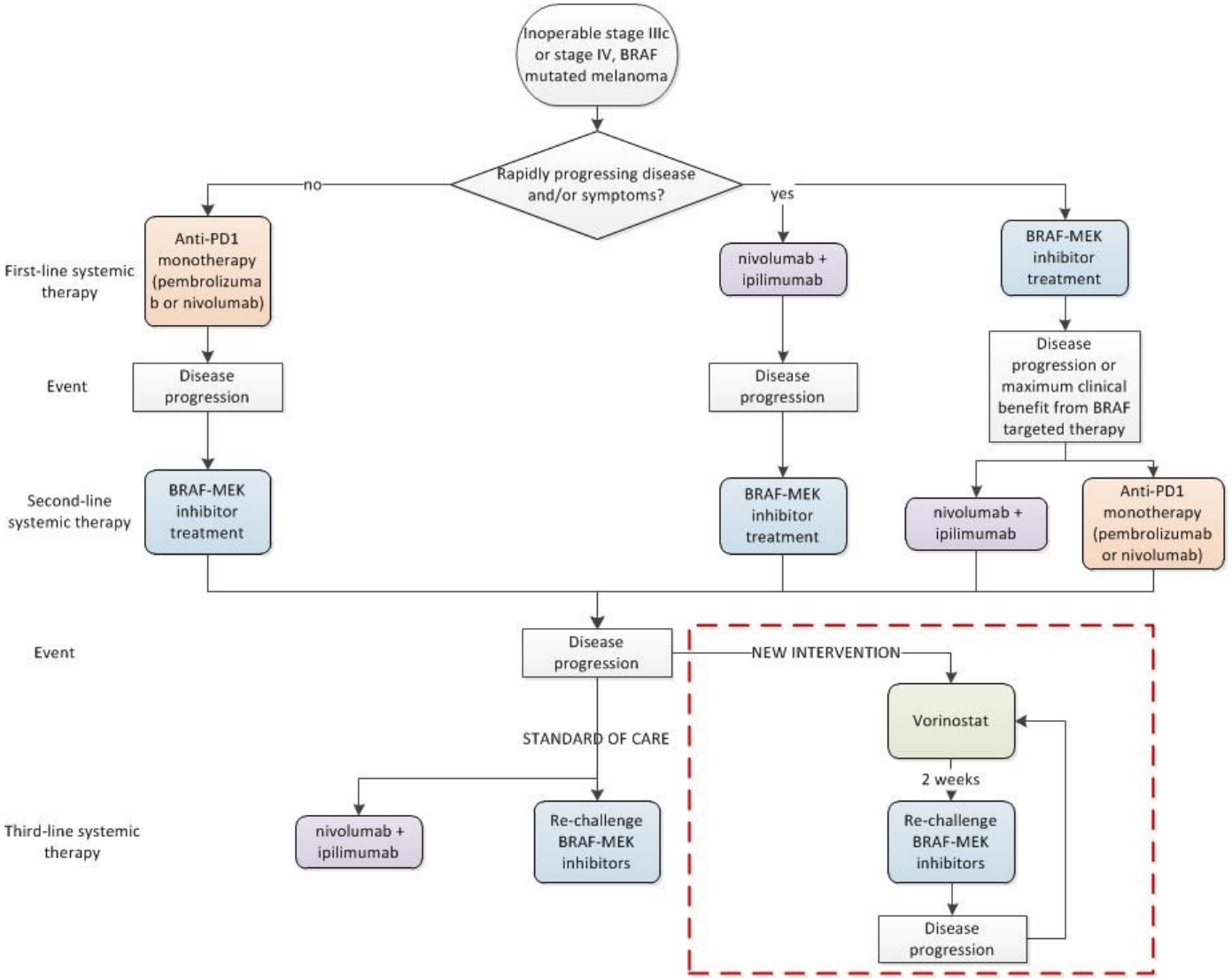
Supplementary materials

Supplementary material 1

Treatment pathway BRAF mutated melanoma stage IIIc / IV, based on NCCN guideline (1) and expert opinion at the NKI-AVL



Supplementary material 2

ICER in costs/QALY in the additional 3 and 12 months survival scenario. Different lengths of treatment cycle are shown at varying drug costs. Green colored cells represent the ICER below € 80,000, yellow colored cells represent the ICER between € 80,000 and € 90,000, red colored cells represent the ICER above € 90,000. The column at the right shows the MRP at the Dutch specific Willingness-To-Pay threshold at each cycle length.

3 months additional median OS

Length of treatment cycle (months)	Costs vorinostat per cycle							Drug cost vorinostat per cycle at a WTP of € 80,000
	€ 0,00	€ 1,000.00	€ 2,000.00	€ 3,000.00	€ 4,000.00	€ 5,000.00	€ 6,000.00	
2	€ -72,877	€ -44,436	€ -15,995	€ 12,447	€ 40,888	€ 69,329	€ 97,771	€ 5,375
3	€ -7,883	€ 11,078	€ 30,039	€ 49,000	€ 67,961	€ 86,922	€ 105,882	€ 4,635
4	€ 24,614	€ 38,835	€ 53,056	€ 67,276	€ 81,497	€ 95,718	€ 109,938	€ 3,895
5	€ 44,113	€ 55,489	€ 66,866	€ 78,242	€ 89,619	€ 100,995	€ 112,372	€ 3,155
6	€ 57,112	€ 66,592	€ 76,072	€ 85,553	€ 95,033	€ 104,514	€ 113,994	€ 2,414
7	€ 66,397	€ 74,523	€ 82,649	€ 90,775	€ 98,901	€ 107,027	€ 115,153	€ 1,674

12 months additional median OS

Length of treatment cycle (months)	Costs vorinostat per cycle							Drug cost vorinostat per cycle at WTP of € 80,000
	€ 0.00	€ 1,000.00	€ 2,000.00	€ 3,000.00	€ 4,000.00	€ 5,000.00	€ 6,000.00	
2	€ 34,237	€ 45,886	€ 57,535	€ 69,184	€ 80,833	€ 92,482	€ 104,131	€ 3,929
3	€ 60,858	€ 68,624	€ 76,390	€ 84,155	€ 91,921	€ 99,,687	€ 107,453	€ 2,465
4	€ 74,168	€ 79,992	€ 85,817	€ 91,641	€ 97,466	€ 103,290	€ 109,114	€ 1,001
5	€ 82,154	€ 86,813	€ 91,473	€ 96,133	€ 100,792	€ 105,452	€ 110,111	€ -462
6	€ 87,478	€ 91,361	€ 95,244	€ 99,127	€ 103,010	€ 106,893	€ 110,776	€ -1,926
7	€ 91,281	€ 94,609	€ 97,937	€ 101,266	€ 104,594	€ 107,922	€ 111,250	€ -3,389

Supplementary material 3

3a Output of the base case analysis when changing the survival parameter values in the vorinostat strategy by steps of 2 months.

	additional median overall survival	Costs	LY	QALY	Incremental costs	Incremental LY	Incremental QALYs	ICER costs/ QALY
SoC	-	€ 127.658	1,12	0,74	-	-	-	-
Vorinostat								
	2	€ 125.377	1,34	0,87	€ -2.281	0,216	0,128	€ -17.768
	4	€ 137.240	1,54	0,99	€ 9.582	0,418	0,244	€ 39.194
	6	€ 147.553	1,72	1,09	€ 19.895	0,604	0,349	€ 56.974
	8	€ 156.582	1,9	1,19	€ 28.924	0,775	0,444	€ 65.199
	10	€ 164.541	2,05	1,27	€ 36.883	0,932	0,529	€ 69.736
	12	€ 171.600	2,2	1,35	€ 43.942	1,076	0,606	€ 72.507

3b Visual representation of the incremental costs (primary axis) and the incremental QALYs (secondary axis) over an additional OS range of 1 to 12 months.